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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,878	10/15/2001	Marsha A. Moses	CMZ-130	3811
26248	7590	11/03/2004	EXAMINER	
NIXON PEABODY LLP			CANELLA, KAREN A	
101 FEDERAL ST			ART UNIT	
BOSTON, MA 02110			PAPER NUMBER	

1642
DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/977,878

Applicant(s)

MOSES ET AL.

Examiner

Karen A Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,6,7,9,10 and 41-48 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1,2,6,7,9,10 and 41-48 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: ____.

DETAILED ACTION

1. Claims 3-5, 8, 11-40 and 49-80 have been canceled. Claims 1, 41, 43 and 46 have been amended. Claims 1, 2, 6, 7, 9, 10, 41-48 are pending and under consideration.

2. The objection to the specification is maintained for reasons of record:

The incorporation of essential material in the specification by reference to a publication is improper. Applicant is required to amend the disclosure on page 1 to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

3. The rejection of Claims 1, 2, 6, 7, 10, 41-48 under 35 U.S.C. 102(b) as being anticipated by Moses et al (Cancer Research, 1998, Vol. 58, pp. 1395-1399) as evidenced by Yan et al (Journal of Biological Chemistry, 2001, Vol. 276, Vol. 40, pp. 37258-37266) is maintained for reasons of record.

Moses et al disclose a method of detecting breast carcinomas by means of detecting high molecular weight complexes comprising MMPs in the urine (Table 2, page 1397 and Figure 1, page 1396) by means of a zymogram containing gelatin (page 1396, under the heading "Data Collection and analysis"). Moses et al disclose that the urine was dialyzed before gel electrophoresis (page 1395, second column, lines 8-12 of the section "Sample Preparation and Substrate Gele Electrophoresis"). Moses et al disclose that detection the 125 kDa molecular weight complex in the urine was indicative of breast cancer (page 1396-1397, bridging sentence and page 1398, second column, lines 39-49).

Yan et al provides evidence that the 125 kDa complex disclosed by Moses et al comprised gelatinase B (MMP-9) and a dimer of the neutrophil associated gelatinase lipocalin (NGAL) (page 37264, first column, lines 53-58). Thus, the detection of the 125kDa complex as

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disclosed by Moses comprises the detection of MMP-9 complexed with two molecules of NGAL.

4. Applicant argues that only one reference is to be relied upon in a 102 rejection. Section 2131.01 of the M.P.E.P. states

Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

- (A) Prove the primary reference contains an "enabled disclosure;"
- (B) Explain the meaning of a term used in the primary reference; or
- (C) Show that a characteristic not disclosed in the reference is inherent.

In the instant rejection, Yan et al is cited to show a characteristic not disclosed in the Moses et al reference, namely, that the 125kD complex of Moses et al is a MMP-9/NGAL complex.

Applicant further argues that there is nothing in Moses et al to lead one of skill in the art to believe that the 125kD species was a complex. This is true but not persuasive. One of skill in the art would be motivated to detect the 125 kD species of Moses et al in order to detect breast cancer. The 125kD complex is the MMP-9/NGAL complexes as taught by Yan et al.

5. The rejection of claims 1, 2, 6, 7, 9, 46 and 48 under 35 U.S.C. 102(b) as being anticipated by Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, Vol. 377, pp. 529-533) is maintained for reasons of record.

Zucker discloses a non-invasive method of diagnosing metastatic genito-urinary tract cancer and gastrointestinal cancer comprising analyzing plasma for the presence of MMP-9 and TIMP-1/MMP-9 complexes by an ELISA immunoassay (page 18). Zucker discloses a non-invasive method of diagnosing breast cancer or gastrointestinal cancer comprising measuring by an EILSA assay MMP-2 complexed with TIMP-2 in plasma (page 15 to page 16, line 6). Zucker discloses that free TIMP-2 has a molecular weight of 22kDa, but is found in complexes of MMPs having molecular weights of up to 150 kDa (page 7, lines 29-34), thus fulfilling the specific embodiment of claim 25.

Kolkenbrock et al disclose that gelatinase B (MMP-9) can exist in three forms: monomer, homodimer and monomer/lipocalin complex. Kolkenbrock et al disclose that about 50% of the monomer/lipocalin complex was found further complexed to TIMP-1 (abstract, lines 1-7).

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Kolkenbrock et al disclose that gelatinase B exhibits three bands on SDS-gel electrophoresis of 220, 130 and 92 kDa. Kolkenbrock et al disclose that the 92 kDa and the 220 kDa forms represent the monomer and the homodimer of the gelatinase B. Kolkenbrock et al t disclose that the 130 kDa form is the monomer complexed with a 25 kDa protein having homology to rat alpha-2-microglobulin protein which was determined to be lipocalin (page 530, first column, lines 28-29). An alternative name for this 25 kDa protein is neutrophil gelatinase associated protein (NGAL) as further evidenced by the abstract of Kjeldsen (Journal of Biological Chemistry, 1993, Vol. 268, pp. 10425-10432). Kolkenbrock et al discloses that TIMP-1 was exclusively bound to the monomer/lipocalin complex (page 532, first column, lines 12-17), thus providing evidence that the MMP9-TIMP-1 complex detected in the method of Zucker further comprised lipocalin because the binding of TIMP-1 requires the complex of MMP-9 and TIMP-1, rather than MMP-9 alone.

6. The rejection of claims 1, 2, 6, 7, 9, 46-48 under 35 U.S.C. 103(a) as being unpatentable over Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, Vol. 377, pp. 529-533) in view of Kerr and Thorpe (Immunochemistry LabFax, 1994, pp. 115-122) is maintained for reasons of record..

Claim 37 embodies the method of claim 46 wherein the enzyme is detected by a radio-immunoassay.

The combination of Zucker et al and Kolkenbrock et al render obvious a method of detecting the enzyme complexes by means of an ELISA assay as applied to claims 1, 2, 6, 7, 9, 11, 46 and 48. the combination does not teach a radioimmunoassay.

Kerr and Thorpe teach the common techniques of radioimmunoassay and ELISA assay (pp. 115-122) as methods of detecting proteins by binding to antibodies carrying a detectable label. Kerr and Thorpe teach that labeling with radioisotopes is usually easy and the conjugates are particularly suitable for many immunochemical procedures (page 115, lines 1-2) It would have been prima facie obvious at the time the invention was made to use a radioimmunoassay for the detection of the enzyme complexes. One of skill in the art would have been motivated to do so by the teachings of Kerr and Thorpe on the easy of radiolabeling antibodies and using the labeled antibodies in immunochemical procedures.

7. The rejection of Claims 1, 2, 6, 7, 9, 43-46, and 48 under 35 U.S.C. 103(a) as being unpatentable over Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, Vol. 377, pp. 529-533) and Moses et al (Cancer Research, 1998, Vol. 58, pp. 1395-1399).

Claims 43-45 are drawn to detection of the enzyme complexes by zymography. The combination of Zucker and Kolkenbrock et al render obvious the detection of the complexes by immunochemical methods. Neither reference teaches the detection of the complexes by zymography.

Moses et al teach that zymography detects a series of enzyme species in a single evaluation and provide additional novel data on cancers which display characteristic zymographic patterns (page 1398, second column, lines 39-46). Moses et al teach the zymogram substrate of gelatin (page 1395, under the heading "Sample Preparation and Substrate Gel Electrophoresis, lines 13-14).

Tsuda et al teach that there is a correlation between gelatinase B enzyme activity and the metastatic potential of tumors (page 38, second column, lines 14-18).

It would have been prima facie obvious at the time the invention was made to detect the gelatinolytic activity of MMP complexes isolated from the plasma of cancer patients. One of skill in the art would have been motivated to do so by the teachings of Moses et al demonstrating the utility of the method in detecting the novel 125 kDa high molecular weight species, and the teachings of Tsuda et al correlating the enzymatic activity of MMP-9 with metastatic potential

8. Applicant argues that because none of the references disclose the MMP-9/NGAL complex, the combination of references does not teach each and every element of the claim. This has been considered but is not persuasive. Kollenbrock et al identify a 130kD complex comprising MMP-9 complexed to lipocalin, which is NGAL. Thus Kollenbrock et al specifically teach the existence of the MMP-9/NGAL complex. Kollenbrock et al further teach that the complex of the monomer/lipocalin complex is further complexed to TIMP-1. Thus, the measurement of TIMP-1/MMP-9 complexes as taught by Zucker et al would inherently comprise a MMP-9/NGAL complex.

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9. The provisional rejection of claims 1, 2, 6, 7, 9-28, 32, 33, 35-48, 77-80 under the judicially created doctrine of obviousness-type double patenting as being anticipated by claims 130, 149-180 of copending Application No. 09/469, 637 is withdrawn in light of applicant's Terminal Disclaimer.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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Karen A. Canella, Ph.D.

10/31/2004


KAREN A. CANELLA PH.D.
PRIMARY EXAMINER